"Approaches towards the Synthesis of Potentially Bioactive Furophenanthraquinones Related to *Salvia* Metabolites and Their Condensed and Doubly Condensed Analogues"

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Summary of Work (5000 Words)

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CONTENTS

Studies towards the synthesis of various condensed and doubly condensed furophenanthraquinones, thienophenanthraquinones and their analogues will be described in the thesis entitled "**Approaches towards the Synthesis of Potentially Bioactive Furophenanthraquinones Related to *Salvia* Metabolites and Their Condensed and Doubly Condensed Analogues".** The thesis will comprise of the following three chapters in which chapter II will further be divided in three subsections IIA, IIB and IIC.

Chapter I: *Studies on the synthesis of some angularly fused novel U-shaped tetracyclic furophenanthraquinones simulating ABCD rings of Isotanshinone-II.*

Chapter IIA: *Suzuki reaction based generalised studies towards the synthesis of 2-(2/3-thineyl)cycloalk-1-ene-1-carbaldehyde derivatives*

Chapter IIB: *Thiophene analogues of Isotanshinone-II nucleus: A novel approach towards the synthesis of phenanthro[4,3-b]thiophene-4,5-dione and phenanthro[3,4-b]thiophene-4,5-dione derivatives.*

Chapter IIC: *Studies towards the synthesis of thienonaphthoquinone derivatives simulating BCD rings of Isotanshinone -II core nucleus.*

Chapter III: *Nuclear modifications in core nucleus of Isotanshinone-II: Synthesis of hitherto unknown bis(heteroannulated)naphthoquinones with antibacterial potential.*

Chapter I

Studies on the synthesis of some angularly fused novel U-shaped tetracyclic furophenanthraquinones simulating ABCD rings of Isotanshinone-II

Introduction

The dried red root of *Salvia miltiorrhiza* Bunge, also known as Danshen or Tanshen is a traditional Chinese medicine, with high safety profile. The crude powder till date is largely used for treatment of viral hepatitis, cardiac and vascular disorder, inflammation, cancer, miscarriage and menstrual disorder, hypertension etc. in many Asian countries with 1000 years of clinical applications.[1] A number of condensed furophenanthraquinones and their di-, tetra- and hexahydro derivatives (fig. 1), have been isolated from *Danshen* and other *Salvia* species, *viz*. *S. glutinosa, S. columbariae* and many of these compounds have been found to display versatile medicinal properties.

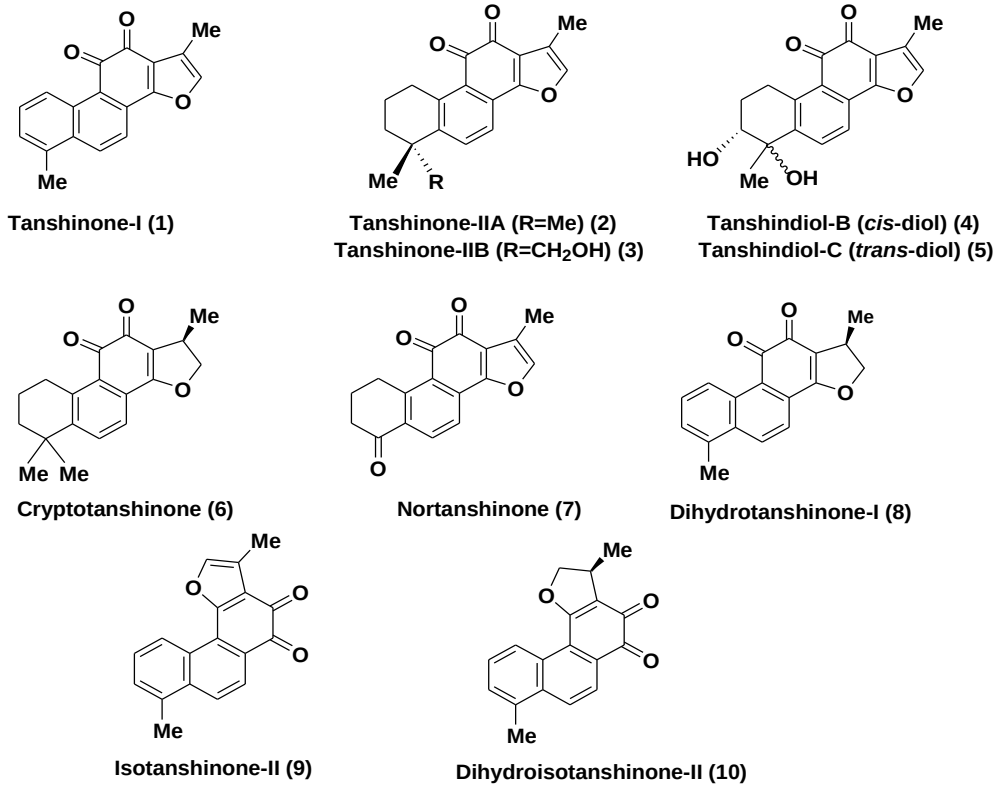
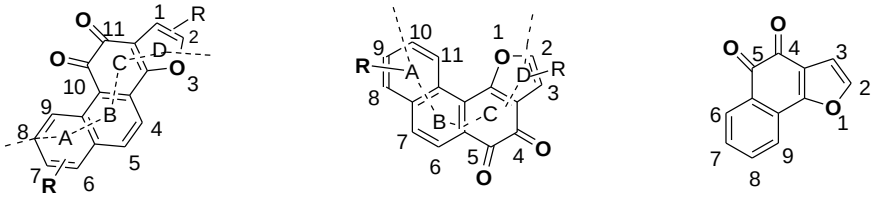


Figure 1: **Some tetracyclic furophenanthraquinone derivatives isolated from *Salvia miltiorrhiza* and *Salvia glutinosa***

Structurally, all the isolated furophenanthraquinones contains a tetracyclic framework either in " S" shaped form (phenanthro[1,2-*b*]furan-10,11-dione derivatives and its di / tetra or hexahydro derivatives) or in "U" shaped form (phenanthro[4,3-*b*]furan-4,5-dione derivatives or its dihydro derivatives) (fig. 2). Both are composed of four rings, including naphthalene or tetrahydronaphthalene part as A and B rings, an *o*-quinine moiety as ring C and a furan or dihydrofuran moiety as ring D, commonly recognised as furophenanthraquinone.[2] Even the tricyclic furonaphthoquinones,[3] simulating BCD rings of tanshinones, show cancer chemo preventive activity and indicate that such type of condensed furophenanthraquinones/ furonaphthoquinones are of general medicinal importance.



"S" shaped furophenanthraquinone "U" shaped furophenanthraquinone tricyclic furonaphthouinone

Figure 2: Core nucleus of "S", "U" shaped furophenanthraquinone and furonaphthoquinone

Various research groups all around the world, have shown interest in synthesis and biological evaluation of mostly tanshinones and their analogues.[4-13] These "S" shaped furophenanthraquinones have shown significant pharmacological activities including cardioprotection,[5] neuroprotection,[6] antileukaemic[7] antioxidative and anticancer activities against different type of cancers.[8-12] Thus in general such condensed furonaphtho/ phenanthraquinones are in the focus as an important field of research in recent times too.

Literature reports on synthesis of tanshinones disclose that most of the synthesis started with either A, B or C ring precursors and ring D was built up in last phase of the synthesis possibly due to unstable nature of the furan ring under acidic condition. Kar and Shaik from our laboratory have developed a method[14] for synthesis of phenanthro[1,2-*b*]furan-10,11-dione and naphtho[1,2-*b*]furan-4,5-dione simulating ABCD/BCD rings of tanshinone nucleus. The method is fashioned on two important key steps: i) construction of aryl-furyl bond *via* Suzuki reaction and ii) generation of the quinone moiety by oxidation of a furophenanthrenol derivative. In this strategy the ring C was built up in latter stage starting

with AB and D ring precursors.The furan ring was found to survive under reaction conditions employed.

Present work

Though in last few decades extensive research work (on synthesis and bioactivity studies) have been done on "S" shaped furophenanthraquinones but work on the same of "U" shaped furophenanthraquinones are limited so far (though Isotanshinone-II, an "U" shaped furophenanthraquinones have also been isolated from *Salvia glutinosa*). Possible reason may be its extremely poor abundance in nature and relatively late discovery.[15] Hence very little is known about such "U" shaped furophenanthraquinones. Recently Kar's group took up a project to synthesise [16] two "U" shaped furophenanthraquinones following the route developed in our laboratory. Our present work is to explore this methodology for the synthesis of more angularly fused furophenathraquinones simulating ABCD core nucleus present in Isotanshinone-II. As usual the two key steps involve i) Suzuki coupling of an aryl halide and furanboronic acid to form aryl-furyl bond and ii) development of *o*-quinone functionality by oxidation of a phenolic moiety (fig. 3).

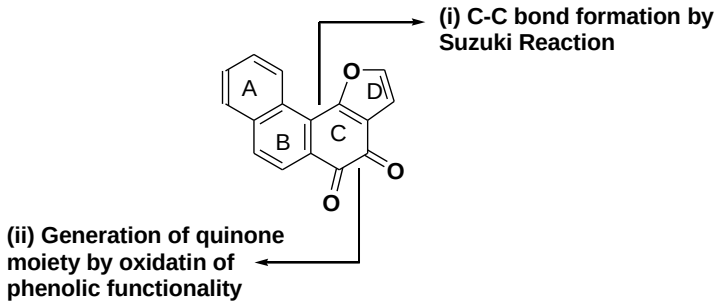
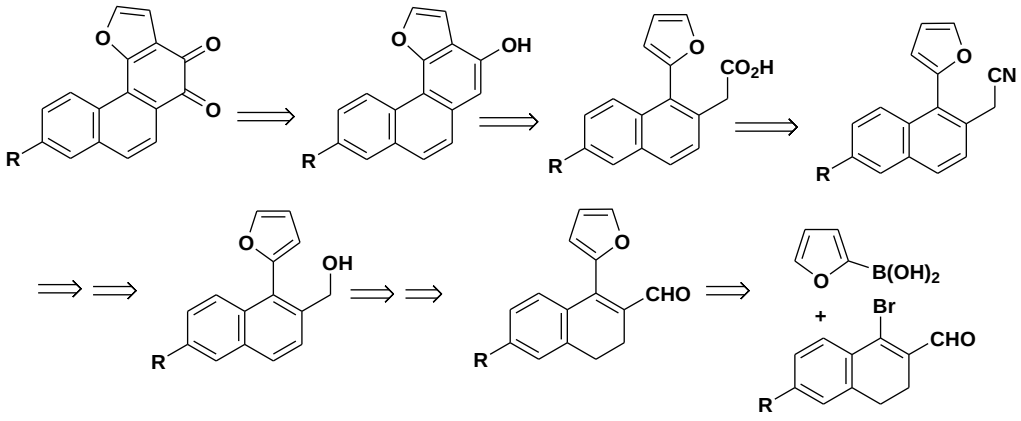


Figure 3: Synthetic strategy for "U" shaped furophenanthraquinone nucleus

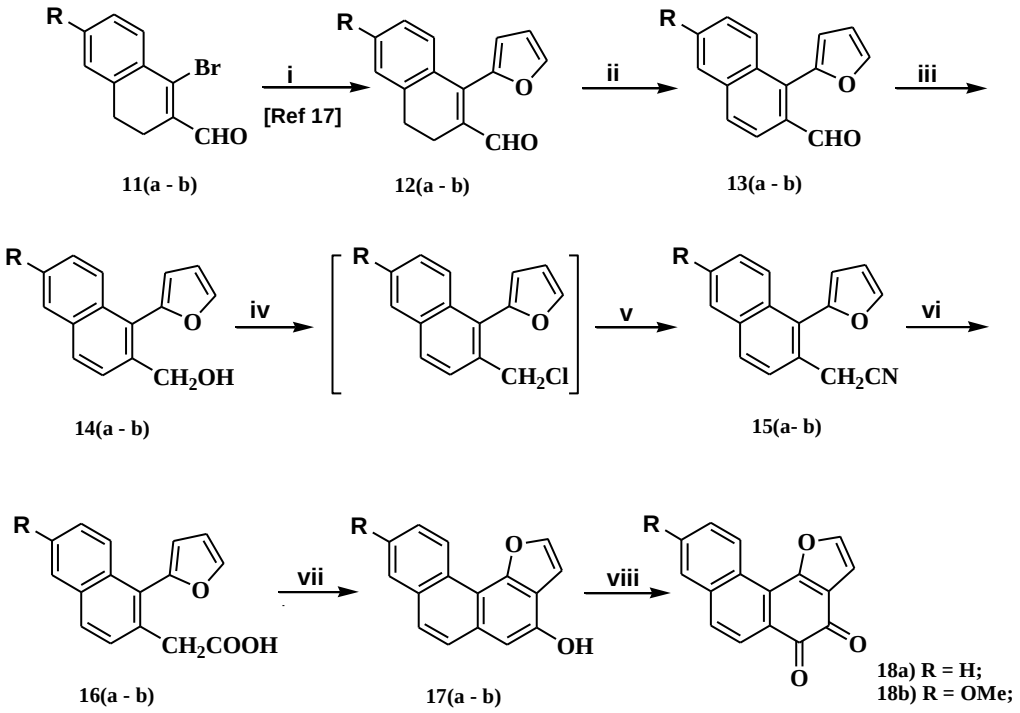


Scheme 1: Retrosynthesis of "U" shaped furophenanthraquinone derivatives

The retrosynthesis depicted in scheme 1 indicates that 3,4-dihydro-1-(2-furyl)-2-napthaldehyde derivatives[17] (already synthesised by reaction of 1-bromo-3,4-dihydro-2-napthaldehyde derivatives and 2-furan boronic acids) may be the suitable precursors for our target molecules.

Result and Discussion:

The synthesis of the target molecules **18**(**a-b**) have been achieved following the general scheme 2 as outlined below:



Reagents and conditions: i) 2-Furanboronic acid, $Pd(PPh_3)_4$, Et_3N, DMF, 100-110 °C, 12-16 hrs, N_2 atm.; ii) DDQ, benzene, reflux, 20-23 hrs, 95-97 %; iii) $NaBH_4$, EtOH, r.t, 2 hrs, 93-95 %; iv) Mesyl chloride, *s*-Collidine, LiCl, DMF, 0 °C-r.t., overnight; v) KCN, DMF, 12 hrs, 74-78 %; vi) Aq. KOH, EtOH, reflux, 32 hrs, 49-53 %; vii) $(CF_3CO)_2O$, CF_3CO_2H, 0 ºC-r.t., overnight, 73-80 %; viii) Fremy's salt, Na_2HPO_4-H_2O, MeOH, overnight, 83-91 %.

Scheme 2: Synthesis of phenanthro[4,3-*b*]furan-4,5-dione derivatives 18(**a-b**)

3,4-Dihydro-1-(2-furyl)-2-napthaldehyde (1**2a**)[17] was subjected to aromatisation with DDQ in refluxing benzene to furnish 1-(2-furyl)-2-naphthaldehyde derivative (**13a**) in 97 % yield. Reduction ($NaBH_4$, EtOH, r.t.) of the aldehyde (**13a**) produced the alcohol (**14a**) in 95 % yield. The alcohol (**14a**) was subsequently converted to the nitrile derivative (**15a**) by

treatment of the alcohol with mesyl chloride, *s*-Collidine and LiCl, in DMF at 0 °C followed by reaction of the resulting chloride with KCN in DMF. The nitrile derivative (**15a**) on hydrolysis (KOH, EtOH-H_2O, reflux) furnished the carboxylic acid (**16a**) as a colourless solid. Then cyclisation of the acid with trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) produced the phenol (**17a**). The phenol was finally oxidised with Fremy's salt [18] to the furophenanthraquinone (**18a**) as a dark red solid. Following a similar sequence of reactions, the *o*-quinone derivative (**18b**) was synthesised from **11b** and 2-furanboronic acid. The compounds were characterised by usual spectroscopic analysis (^{1}H NMR, ^{13}C NMR, IR, HRMS). Tentative assignments of ^{1}H NMR chemical shifts (δ, ppm) and splitting pattern of the furophenanthraquinones **18**(**a-b**) are described in fig. 4.

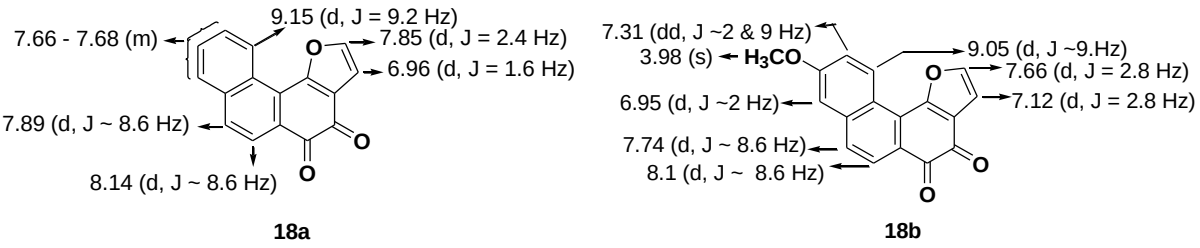


Figure 4: **Tentative assignments of ^{1}H NMR chemical shifts of compounds 18**(**a-b**)

Conclusion

In this chapter, we have achieved the synthesis of two "U" shaped novel furophenanthraquinone derivatives **18a** (phenanthro[4,3-*b*]furan-4,5-dione) and **18b (**9-methoxyphenanthro[4,3-*b*]furan-4,5-dione). Biophysical studies of the synthesised compounds are under progress as collaborative work with other group.

References:

1. a) T. O. Cheng, *Int. J. Cardiol.* **2007**, *121(1)*: 9-22. b) X. Wang, S. L. Morris-Natschke, K. H. Lee, *Med. Res. Rev.* **2007**, *27*: 133. c) Y. Wu, Z. Y. Ni, Q. W. Shi, M. Dong, H. Kiyota, Y. C. Gu, B. Cong, *Chem. Rev.* **2012**, *112*, 5967. d) C. Y. Su, Q. L. Ming, K. Rahman, T. Han, L. P. Qin, *Chinese J. Nat. Med.* **2015**, *13*, 163. e) Z. Li, S. Xu, P. Liu, *Acta Pharmacol. Sin.* **2018**, 1.

2. B. Q. Wang, *J. Med. Plant Res.* **2010**, *4*, 2813.

3. H. Lin, L. Zheng, S. Li, B. Xie, B. Cui, A. Xia, Z. Lin, *Phytother. Res.* **2018**, 1.

4. a) Y. Dong, S. L. Morris-Natschke, K. H. Lee, *Nat. Prod. Rep.* **2011**, 28(3), 529. b) N. Wu, W. C. Ma, S. J. Mao, Y. Wu, H. Jin, *J. Nat. Prod.* **2017**, *80*, 1697. c) R. L. Danheiser, D. S. Casebier, F. Firooznia, *J. Org. Chem.* **1995**, *60*, 8341 and reference sited there in. d) J. Lee, J. K. Snyder, *J. Am. Chem. Soc.* **1989**, *111*, 1522. e) J. Lee, J. K. Snyder, *J. Org. Chem*. **1990**, *55*, 4995. f) Y. Y. Jiang, Q. Li, W. Lu, J. C. Cai, *Tetrahedron Lett.* **2003**, *44*, 2073.

5. Y. L. Qin, L. Chen, W. He, M. Su, Q. Jin, Z. Fang, P. K. Ouyang, K. Guo, *J. Asian Nat. Prod. Res.* **2018**, *20(2)*, 139.

6. S. Gao, Z. Liu, H. Li, P. J. Little, P. Liu, S. Xu, *Atherosclerosis* **2012**, *220(1)*, 3.

7. K. Dong, W. Xu, J. Yang, H. Qiao, L. Wu, *Phytother. Res.* **2009**, *23(5)*, 608.

8. M. A. Mosaddik, *Phytomedicine* **2003**, *10*, 682.

9. a) I. T. Nizamutdinova, G. W. Lee, J. S. Lee, M. K. Cho, K. H. Son, S. J. Jeon, S. S. Kang, Y. S. Kim, J. H. Lee, H. G. Seo, K. C. Chang, H. Kim, *J. Carcinogenesis* **2008**, *29*, 1885. b) X. Chen, J. Guo, J. Bao, J. Lu, Y. Wang, *Med. Res. Rev.* **2014**, *34*, 768. c) D. Wang, D. Xu,Y. Sun, Y. Wu, L. Ma, J. Duan, *Glycoconj. J.* **2017**, *34*, 3.

10. P. Zhao, S. T. Soukup, J. Hegevoss, S. Ngueu, S. E. Kulling, P. Diel, *Planta Med.* **2015,** *81(07):* 578.

11. M. S. Xiao, R. H. Zuo, A. H. Dam, D. Huang, S. Zhang, *Molecular medicine report* **2016**, 13: 3036.

12. L. W. Zeng, C. X. Zhou, J. D. Liu, C. Liu, J. X. Mo, A. F. Hou, L. S. Gan, *Nat. Prod. Res.* **2016**, 1.

13. a) F. Wang, H. Yang, S. Yu, Y. Xue, Z. Fan, G. Liang, M. Geng, A. Zhang, C. Ding, *Org. Biomol. Chem.* **2018**, *16*, 3376. b) L. Q. Nan, H. Z. Peng, G. Q. Lan, Z. Z. Er, Y. Y. Han, H. Long, C. K. Li, J. W. Xin, *Chin. J. Nat. Med.* **2018**, ***16***(2), 0113. c) N. Wu, W. C. Ma, S. J. Mao, Y. Wu, H. Jin, *J. Nat. Prod.* **2017**, *80*, 1697. d) F. Chen, L. Li, D. D. Tian, *Bio. Med. Res. Int.* **2017**, Article ID 9868694.

14. F. H. Shaik, G. K. Kar, *Beilstein J. Org. Chem.* **2009**, *5*, No. 47.
15. G. Nagy, G. Gnther, I. Mathe, G. Blunden, M. Yang, T. A. Crabb, *Photochemistry* **1999**, *52*, 1105.
16. K. Samanta, *Ph.D. Thesis*: *Derivatives of phenanthrenes and phenanthraquinones: Synthesis via Suzuki coupling and other reactions*, **2011**, University of Calcutta, Kolkata, India, Chapter-3.
17. K. Samanta, G. K. Kar, A. K. Sarkar, *Tetrahedron Lett.* **2012**, *53*, 1376.
18. H. Zimmer, D. C. Lankin, S. W. Horgan, *Chemical Review* **1971**, 71, 229.

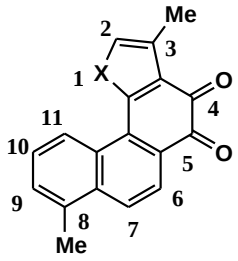
Oral presentation:

"***Model studies towards the synthesis of Isotanshinone-II: General method for synthesis of some angularly fused novel "U" Shaped furoquinones simulating ABCD rings of Isotanshinone-II***": Aparna Sarkar, Rumpa Das, Khokan Samanta, Gandhi K. Kar; *Proceedings of the* National Symposium *on Recent Advances in Chemistry and Industry (***2015***);* Indian Chemical Society, Calcutta University, Kolkata.

Chapter II

Introduction

Second chapter of the thesis describes the synthesis of thiophene analogues (fig. 1) of "U" shaped furophenanthraquinones simulating ABCD rings of Isotanshinone-II, following the methodology as used in previous chapter. Such thiophene analogues however are not known as natural products. To our surprise, the synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives are not available in the literature, though in connection with the study of the mutagenic activities of *trans* dihydrodiol derivatives of phenanthro[3,4-*b*]thiophene and phenanthro[4,3-*b*]thiophene, synthesis of phenanthro[3,4-*b*]thiophene-8,9-dione, phenanthro[4,3-*b*]thiophene-6,7-dione intermediates have been reported.[1-3]

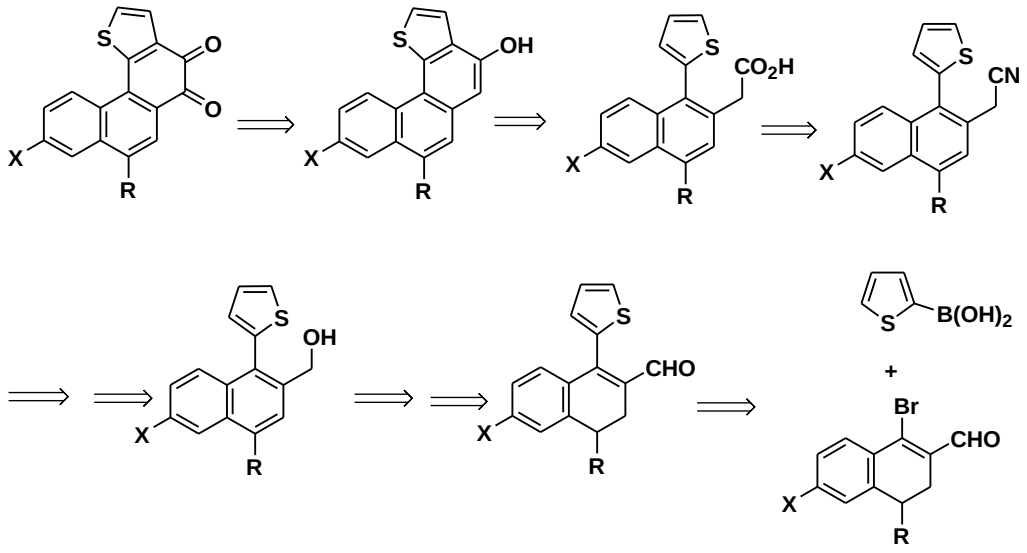


X= O (Isotanshinone-II)

X= S (thiophene analouge of Isotanshinone-II)

Figure 1: Isotanshinone-II and its thiophene analogue

As usual, retrosynthesis of the phenanthro[4,3-*b*]thiophene-4,5-dione derivatives (thienophenanthraquinones) reveals that the synthesis may be achieved from 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde and 2-thiopheneboronic acid (scheme 1).



Scheme 1: Retrosynthesis of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives

In this connection first of all a detailed studies of Suzuki reaction between β-bromo-α,β-unsaturated carbaldehydes and thiopheneboronic acids were necessary. Thus the chapter II was divided in three subsections IIA, IIB and IIC, in which chapter IIA described a generalized studies on Suzuki reaction of various β-bromo-α,β-unsaturated carbaldehydes with 2/3-thiopheneboronic acid

Chapter IIA

Suzuki reaction based generalised studies towards the synthesis of 2-(2/3-thineyl)cycloalk-1-ene-1-carbaldehyde derivatives

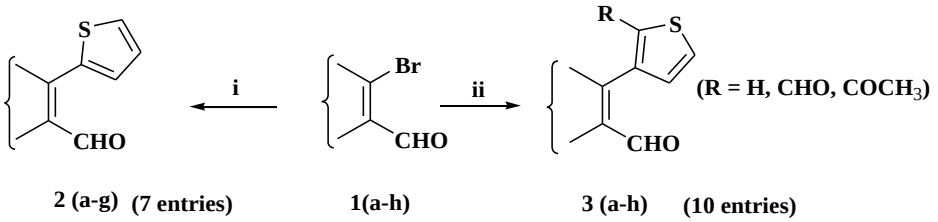
Present work

For the synthesis of various thienophenanthraquinones like phenanthro[4,3-*b*]thiophene-4,5-dione or phenanthro[3,4-*b*]thiophene-4,5-dione derivatives, various 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives might be the possible building blocks. Though one or two isolated examples of the synthesis of such type of thienylcarbaldehyde are reported in the literature,[4,5] no specific study has yet been made. Kar's group developed a generalised route for the synthesis of β-(2-furayl)-α,β-unsaturated aldehydes.[6] As an extension of the methodology, in this chapter, a comprehensive studies on the synthesis of 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehydes have been taken up *via* Pd(0) catalysed Suzuki reaction[7] of various 2-bromocycloalk-1-ene-1-carbaldehydes[6,8,9] with 2/3-thiopheneboronic acids. The method is relatively simple, short and high-yielding and the products have great potential as building blocks in synthetic organic chemistry.

Result and discussion

Thus the bromoaldehydes **1**(**a-h**) were subjected to Suzuki coupling with 2-thiopheneboronic acid or 3-thiopheneboronic acid derivatives in presence of $Pd(PPh_3)_4$ cat., Et_3N in DMF at 110-120 °C under N_2 atmosphere, and the respective thienylated aldehydes were obtained in good to excellent yields (scheme 2). As many as seventeen 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives **2**(**a-g**) and **3**(**a-h**) were obtained (table 1) from eight β-bromo-α,β-unsaturated aldehyde derivatives **1**(**a-h**) and four thiopheneboronic acids [2-

thiophenelboronic acid (**A**), 3-thiopheneboronic acid (**B**), 2-formyl-3-thiopheneboronic acid (**C**) and 2-acetyl-3-thiopheneboronic acid (**D**)] used to study the Suzuki reactions.

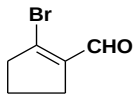
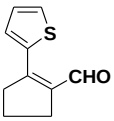
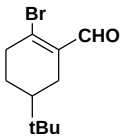
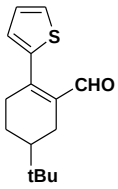
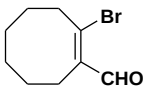
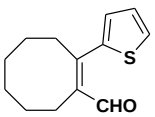


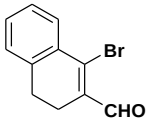
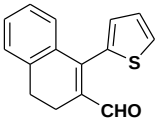
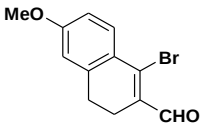
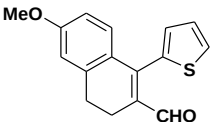
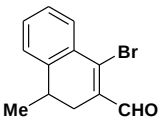
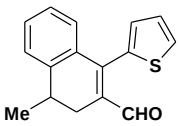
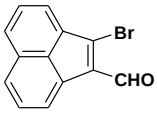
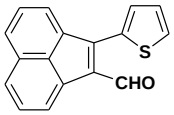
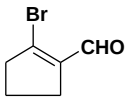
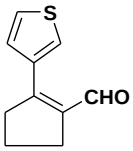
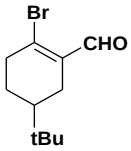
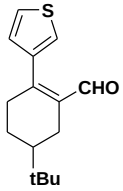
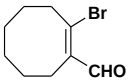
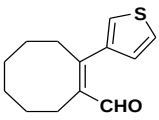
Reagents and conditions: i) 2-thiopheneboronic acid, $Pd(PPh_3)_4$ (1 mol %), Et_3N, DMF, 110-120 ^oC, 6.5-7 hrs under N_2 atm., 70-80 %; ii) optionally substituted 3-thiopheneboronic acid, $Pd(PPh_3)_4$ (1 mol%), Et_3N, DMF, 110-120 ^oC, 4-12 hrs under N_2 atm., 55-90 %.

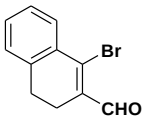
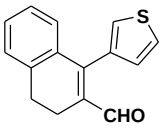
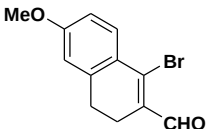
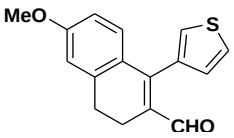
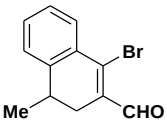
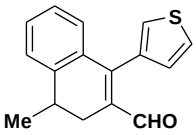
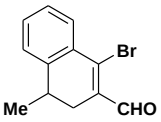
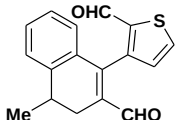
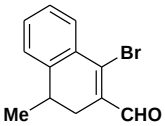
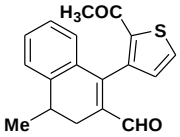
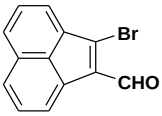
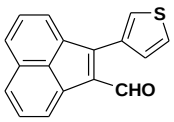
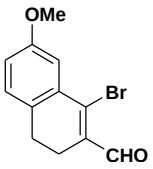
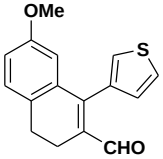
Scheme 2: Suzuki reactions of β-bromo-α,β-unsaturated aldehydes

In general, the yields of the Suzuki reactions, with 3-thiopheneboronic acid were higher than those with 2-thiopheneboronic acids. The compounds have been characterised by usual spectroscopic methods.

Table-1

Entry No.	β-Bromo-α,β-unsaturated aldehyde	Boronic acid	Product	Time (hrs)	% yield
1	 **1a**	A	 **2a**	6	72
2	 **1b**	A	 **2b**	7	73
3	 **1c**	A	 **2c**	6	80

4	 **1d**	A	 **2d**	7	72
5	 **1e**	A	 **2e**	6.5	70
6	 **1f**	A	 **2f**	7	82
7	 **1g**	A	 **2g**	7	78
8	 **1a**	B	 **3a**	4	78
9	 **1b**	B	 **3b**	5.5	80
10	 **1c**	B	 **3c**	5	86

11	 **1d**	B	 **3d**	6.7	80
12	 **1e**	B	 **3e**	6	77
13	 **1f**	B	 **3f$_1$**	5	90
14	 **1f**	C	 **3f$_2$**	12	55
15	 **1f**	D	 **3f$_3$**	10	59
16	 **1g**	B	 **3g**	7	82
17	 **1h**	B	 **3h**	7	88

Tentative assignment of ^{1}H NMR chemical shifts (δ, ppm) and splitting patterns of some of the representative thienylated products **2e**, **2f** and **3h** are depicted in fig. 2.

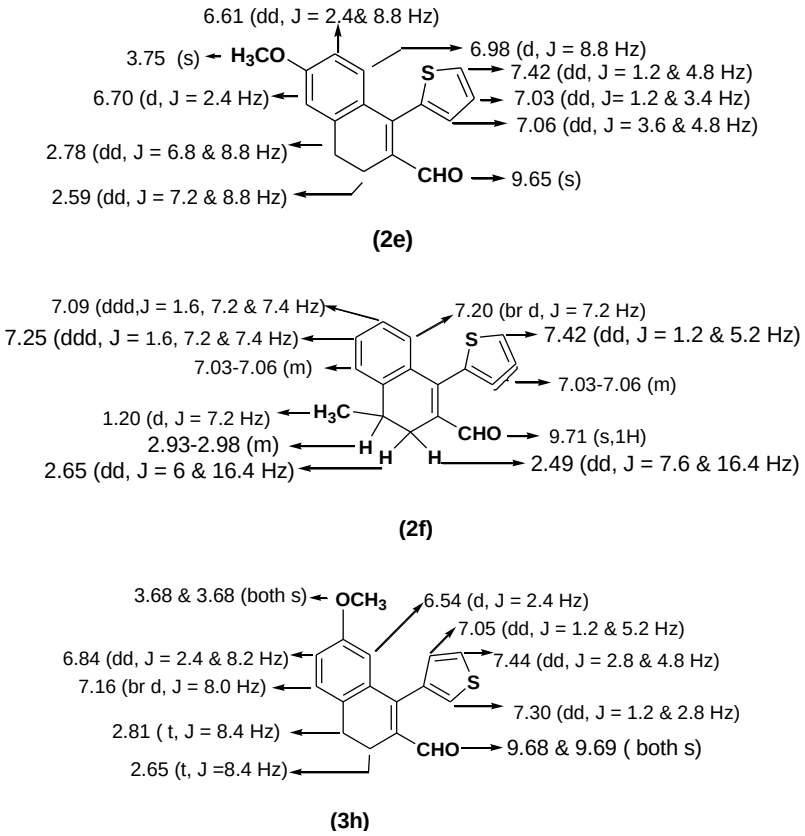


Figure 2: **Tentative assignment of ^{1}H NMR chemical shifts of compounds 2e, 2f and 3h**

Conclusion

We have developed a novel method for the synthesis of 2-(2/3-thienyl)cycloalk-1-ene-1-cabalaldehyde derivatives. The method has pronounced prospective for synthesis of small molecules such as condensed tetracyclic thienophenanthraquinones, tricyclic thienonaphthraquinones and might also be useful for the synthesis of condensed thienophenanthrenol intermediates as bioisosters of the corresponding mutagenic polynuclear hydrocarbons. In compounds such as **3f$_2$** and **3f$_3$**, the two carbonyl functionalities can further be coupled or condensed and thus can be good precursors for synthesis of polycyclic thiaarene derivatives too.

Publication:

"A Suzuki-Coupling-Based Generalized Route for the Synthesis of 2-(2/3-thienyl)-cycloalk-1-ene-1-carbaldehydes as Precursors for Condensed Thienophenanthraquinones" Aparna Sarkar, Rumpa Das, Gandhi K. Kar; **Synlett 2018**, *29*, 344-348.

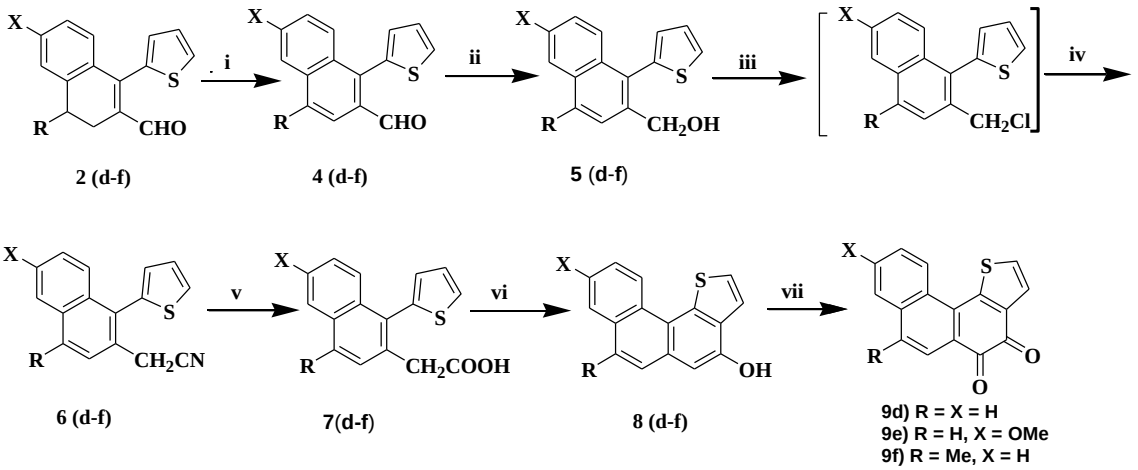
Chapter IIB

Thiophene analogues of Isotanshinone-II nucleus: A novel approach towards the synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione and phenanthro[3,4-*b*]thiophene-4,5-dione derivatives

Present work

In this part of the chapter, we have explored some the thienylated compounds **2**(**d-f**) and **3h**, synthesised in chapter IIA, for the synthesis of hitherto unknown phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **9**(**d-f**) as well as 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (**15**) following the scheme 3 and scheme 4 respectively. The compounds **9**(**d-f**), as thiophene analogues, resembles the ABCD ring system of Isotanshinone-II.

Thus 1-(2-thienyl)-3,4-dihydronaphthalene-2-carbaldehyde (**2d**) was aromatised to 1-(2-thienyl)naphthalene-2-carbaldehyde (**4d**) in 97 % yield on refluxing with DDQ in dry benzene. The aldehyde **4d** was then reduced with $NaBH_4$, EtOH to the alcohol **5d** in 97 % yield. Side chain homologation of $-CH_2OH$ to $-CH_2CO_2H$ was achieved in four steps to obtain **7d** in overall good yields. Thus compound **5d** on reaction with MsCl, LiCl, *s*-collidine at 0-5 ^oC afforded the crude chloride intermediate which on reaction with KCN in DMF furnished the nitrile derivative (**6d**) in very good yield. The nitrile (**6d**) was then hydrolysed (KOH, EtOH-water, reflux) to the acid (**7d**) in moderate yield. The acid (**7d**) on cyclisation with TFAA-TFA mixture furnished the phenanthro[4,3-*b*]thiophen-4-ol (**8d**) in excellent yield. Oxidation of **8d** with Fremy's salt[10] in MeOH, aq. Na_2HPO_4 buffer at 0-5 °C afforded phenanthro[4,3-*b*]thiophene-4,5-dione (**9d**) as dark violet solid.

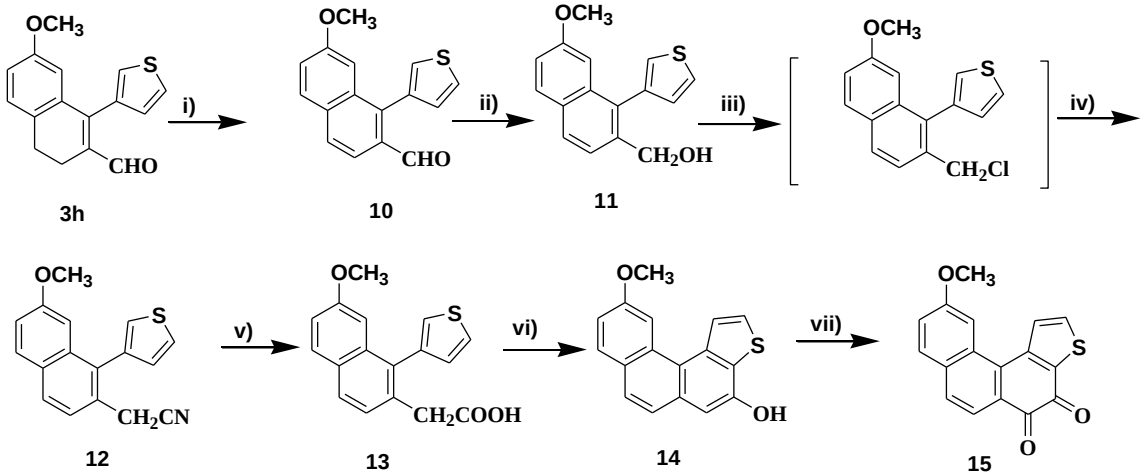


Reagents and conditions : i) DDQ, benzene, reflux, 20-24 hrs, 87-97 %; ii) $NaBH_4$, EtOH, r.t., 2 hrs, 94-97 %; iii) Mesyl chloride, *s*-Collidine, LiCl, DMF, 0-5 °C, overnight; iv) KCN, DMF, overnight, 63-82 %; v) Aq KOH, EtOH, reflux, 20-30 hrs, 44-52 %; vi) TFAA, TFA, 0-5 °C, overnight, 64-87 %; vii) Fremy's salt, aq. Na_2HPO_4 buffer, MeOH, 0-5 °C, overnight, 77-97 %.

Scheme 3: Synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives

Following a similar sequence of reactions, two more phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **9(e-f)** have been synthesised starting from 3,4-dihydro-6-methoxy-1-(2-thienyl)naphthalene-2-carbaldehyde (**3e**) and 3,4-dihydro-4-methyl-1-(2-thienyl)naphthalene-2-carbaldehyde (**3f**) respectively (scheme 3).

An another novel thienophenanthraquinone (**15**) (10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione) was also synthesised starting from a 3,4-dihydro-1(3-thienyl)-7-methoxynaphthalene-2-carbaldehyde (**1h**) [8,9] following a similar pathway too (scheme 4).



Reagents and conditions : i) DDQ, Benzene, reflux, 20 hrs, 97 %; ii) $NaBH_4$, EtOH, r.t, 2 hrs, 94 %; iii) Mesyl chloride, *s*-Collidine, LiCl, DMF, 0-5 °C, overnight; iv) KCN, DMF, overnight, 80 %; v) Aq KOH, EtOH, reflux, 22 hrs, 44 %; vi) TFAA, TFA, 0-5 °C, overnight, 92 %; vii) Fremy's salt, Na_2HPO_4-H_2O, MeOH, 0-5 °C, overnight, 87 %.

Scheme 4: Synthesis of 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (15)

All the compounds have been characterised by usual spectroscopic methods. Tentative assignment of ^{1}H NMR spectral data of the representative thienophenanthraquinones **9**(**d**-f) and **15** are depicted in fig. 3.

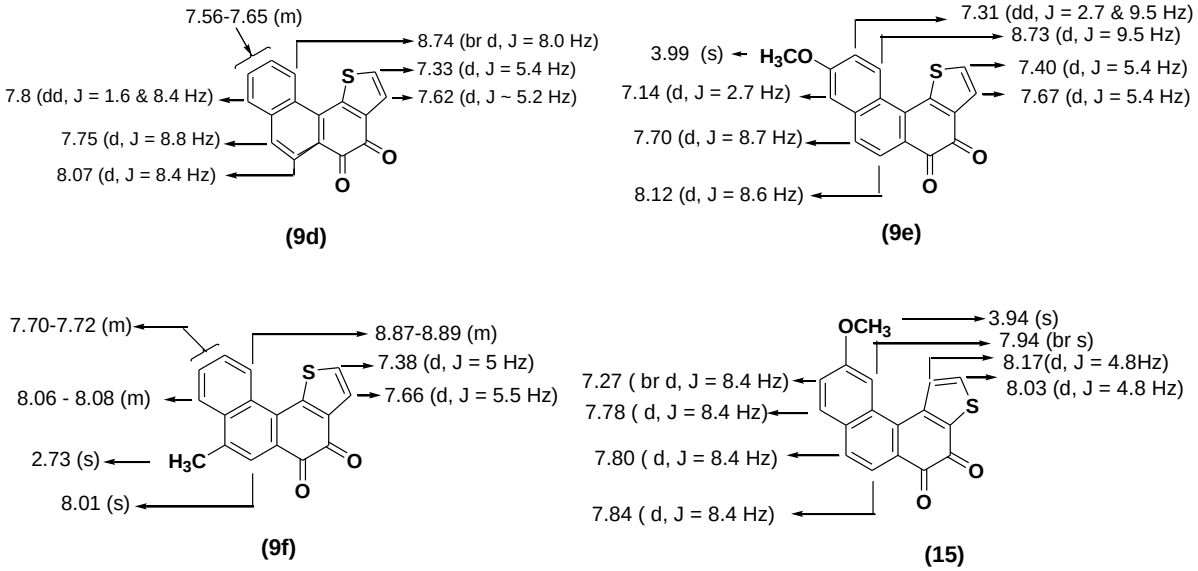


Figure 3: Tentative assignment of ^{1}H NMR spectral data of 9(d-f) and 15

Conclusion

In conclusion, four novel phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **9**(**d-f**) and 10-methoxy-phenanthro[3,4-*b*]thiophene-4,5-dione (**15**) have been synthesised as an extension of the work described in chapter I. The yields in most of the steps are very good to excellent. To our belief, the process is much easier and not too lengthy. The method is a general one and each of the 1-(2/3-thienyl)-3,4-dihydronaphthalene-2-carbaldehyde derivatives as reported in this chapter IIA, may lead to some novel condensed thienophenanthraquinone derivatives. The compounds may be unique for study of the biological as well as biophysical activities.

Publication:

"Thiophene Analogue of Isotanshinone-II Nucleus: A Novel Approach towards the Synthesis of Phenanthro[4,3-b]thiophene-4,5-dione and Phenanthro[3,4-b]thiophene-4,5-dione Derivatives" Aparna Sarkar, Rumpa Das, and Gandhi K. Kar; **ChemistrySelect 2018**, 3, 11422-11426**.**

Chapter IIC

Studies towards the synthesis of thienonaphthoquinone derivatives simulating BCD rings of Isotanshinone-II core nucleus

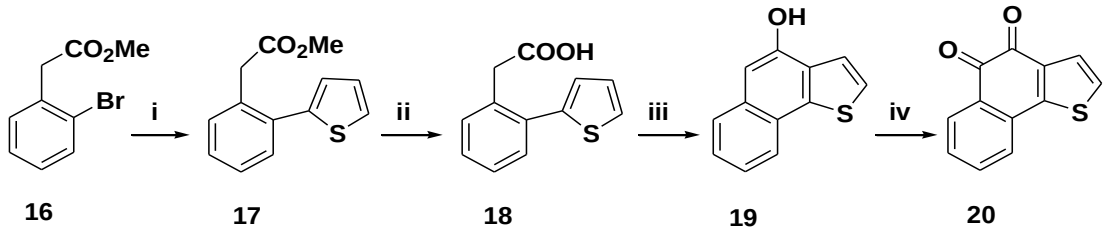
Present work

Various naphthoquinones condensed with heterocyclic moieties like furan, dihydrofuran, thiophene, pyran etc are well known for their antitumour activities.[11] Thienonaphthoquinones, however are not available from natural sources. Nevertheless, there are some reports on the synthesis of both furonaphthoquinone and thienonaphthoqunone derivatives.[12-16] Notably studies on the biological activities of naphtho[2,1-*b*]thiophene-4,5-diones, naphtho[1,2-*b*]thiophene-4,5-diones and naphtho[2,3-*b*]thiophene-4,9-diones are of special importance as some of such derivatives show antitumor, antibacterial or antimicrobial activities, and are highly active even towards the doxorubicin resistant cell lines like MDA-MB435 (melanoma), SF-295 (glioblastoma), IGROV (ovarian) and human cell lines.[17-23] Already, a synthetic route for the furonaphthoquinones have been developed in our laboratory by Kar's group.[24, 25] Following the same protocol, in chapter IIC, synthesis of two thienonaphthoquinones, naphtho[1,2-*b*]thiophene-4,5-dione and naphtho[2,1-*b*]thiophene-4,5-dione have been described staring from commercially available methyl 2-(bromophenyl)acetate (**16**) and 2/3-thiopheneboronic acids.

Result and discussion

Pd(0) catalysed Suzuki coupling of the ester 1**6** with 2-thiopheneboronic acid produced methyl 2-(2-thienyl)phenylacetate (**17**) as a pale yellow oil in good yield. Subsequent hydrolysis of **17** to the acid (**18**) followed by cyclisation to the naphtho[1,2-*b*]thiophen-4-ol

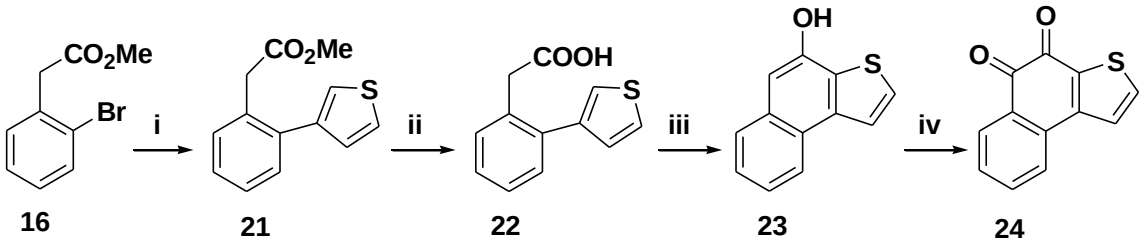
(**19**) in excellent yield. Oxidation of the intermediate phenol **19** with Fremy's salt furnished the target molecule **20** in very good yield (scheme 5).



Reagents and conditions: (i) 2-thiopheneboronic acid, Et_3N, DMF, $Pd(PPh_3)_4$, 110 °C, nitrogen, 6 hrs, 65 %; (ii) KOH, EtOH, H_2O, reflux, 12 hrs, 78 %; (iii) TFAA, TFA, 0 °C, overnight, 80 %; (iv) Fremy's salt, 1/6 M aq. Na_2HPO_4, MeOH, r.t., overnight, 72 %.

Scheme 5: Synthesis of naphtho[1,2-*b*]thiophene-4,5-dione.

Similarly, naphtho[2,1-*b*]thiophene-4,5-dione (**24**) was prepared starting from same ester **16** and 3-thiopheneboronic acid (scheme 6).



Reagents and conditions: (i) 3-thiopheneboronic acid, Et_3N, DMF, $Pd(PPh_3)_4$, 110 °C, nitrogen, 5 hrs, 72 %; (ii) KOH, EtOH, H_2O, reflux, 10 hrs, 83 %; (iii) TFAA, TFA, 0 °C, overnight, 75 %; (iv) Fremy's salt, MeOH, 1/6 M aq. Na_2HPO_4, r. t., overnight, 86 %.

Scheme 6: Synthesis of naphtho[2,1-*b*]thiophene-4,5-dione

Tentative interpretation of ^1H NMR spectral data of the thienonaphthoquinones (**20** and **24)** are presented in fig. 4.

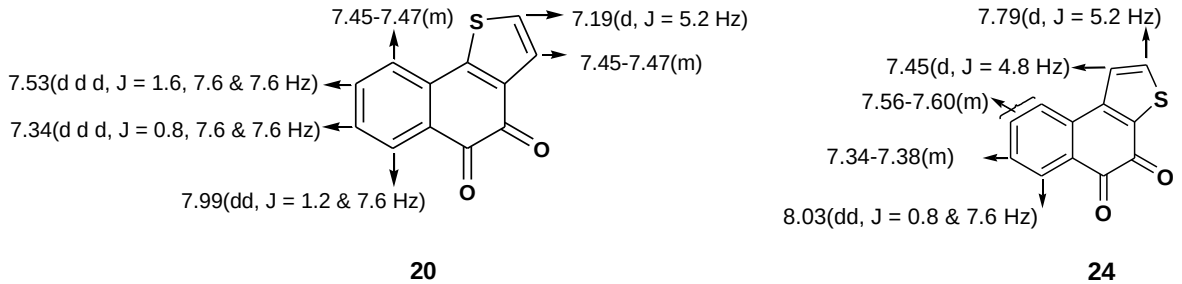


Figure 4: Tentative assignments of ^{1}H NMR chemical shift of the *o*-quinones 20 and 24

Conclusion

In conclusion we have synthesised two thienonaphthoquinone derivatives simulating BCD ring of Isotanshinone-II core nucleus *via* a novel and very short synthetic route. Biophysical and biological studies are under progress as collaborative work.

Reference

1. S. Kumar, P. A. Ruben, A. Kumar, *Polycyclic Aromatic Compounds*, **2004**, *24*, 4-5, 289.
2. S. Kumar, P. A. Ruben, A. J. Kumar, *J. Heterocyclic Chem*. **2005**, *42*, 1345.
3. S. Kumar, *J. Org. Chem*. **2002**, 67, 8842.
4. M. L. N. Rao, D. Banerjee, R. J. Dhanorkar, *Synlett* **2011**, *No. 2*, 273.
5. S. Hesse, G. Kirsch, *Synthesis* **2001,** *No. 5*, 755.
6. K. Samanta, G. K. Kar, A. K. Sarkar, *Tetrahedron Lett*. **2008**, *49*, 1461.
7. N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
8. J. Gogoi, P. Gogoi, R. C. Boruah, *Eur. J. Org. Chem.* **2014**, *16*, 3483.
9. S. S. Moleele, J. P. Michael, C. B. de Koning, *Tetrahedron* **2006,** *62*, 2831.
10. H. Zimmer, D. C. Lankin, S. W. Horgan, *Chemical Review* **1971**, *71*, 229.
11. J. Acuna, J. Piermattey, D. Caro, S. Bannwitz, L. Barrios, J. Lopez, Y. Ocampo, R. V. Reyes, F. Aristizabal, R. Gaitan, K. Muller, L. Franco, *Molecules* **2018**, *23*, 186 .
12. J. Lee, J. K. Snyder, *J. Org. Chem*. **1990**, *55*, 4995.
13. A. F. M Brandao, A. B. d Oliveira, V. Snieckus, *Tetrahedron Lett*. **1993**, *34*, 2437.
14. K. Yoshida, A. Hayashi, T. Mamura, **2008,** 28 Aug., *Jpn. Kokai Tokkyo Koho 2008195749.*
15. S. Kurokawa, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1454.
16. K. Kabayashi, S. Yamane, K. Miyamoto, O. Morikawa, H. Konishi, *Heterocycles*, **2005**, *65(12)*, 2973.
17. T. Konoshima, M. Kozuka, *J. Nat. Prod.* **1989**, *52*, 987.
18. J. Valderrama, A. Fournet, C. Valderrama, S. Bastias, C. Astudillo, R. d. Arias, A. Inchausti, G. Yaluff, *Chem. Pharm. Bull.* **1999**, *47*, 1221.
19. K. Kobayashi, S. Yamane, K. Miyamoto, O. Morikawa, H. Konishi, *Heterocycles* **2005**, *65(12)*, 2973.
20. S. Shinamura, E. Miyazaki, K. Takimiya, *J. Org. Chem.* **2010**, *75*, 1228.

21. S. Shinamura, I. Osaka, E. Miyazaki, A. Nakao, M. Yamagishi, J. Takeya, K. Takimiya, *J. Am. Chem. Soc.* **2011**, *133*, 5024.
22. I. G. Monterrey, P. Campiglia, C. Aquino, A. Bertamino, B. Maresca, E. Novellino, *J. Med. Chem.* **2011**, *54*, 4077.
23. P. Dutta, W. Yang, W. Lee, L. N. Kang, S. H. Lee, *J. Mat. Chem.* **2012**, *22*, 10840.
24. F. H. Shaik, G. K. Kar, *Beilstein J. Org. Chem.* **2009**, *5*, No. 47.
25. M. Rakshit, *Ph.D. Thesis*: *Studies on the synthesis of condensed heterocycles via alkynylation, arylation and olefination of suitable β-halo-α,β-unsaturated aldehyde intermediates*, **2016**, University of Calcutta, Kolkata, India, chapter-4.

Chapter III

Nuclear modifications in core nucleus of Isotanshinone-II: Synthesis of hitherto unknown bis(heteroannulated)naphthoquinones with antibacterial potential

Introduction

Condensed furo/thienonaphthoquinones are known to act as antitumor and antibacterial agents.[1] Moreover, naphthothiophene derivatives are used in solar cells and subjugated in the preparation of organic nanotubes for its unique semiconducting properties. Thus condensed naphthothiophene/furans and their quinone derivatives are subject matter of studies for organic synthesis or materials research.[2-6]

In the earlier chapter, synthesis of some phenanthro[4,3-*b*]thiophene-4,5-dione derivatives have been reported as nuclear analogues of Isotanshinone-II core nucleus. In those compounds, ring D of Isotanshinone-II has been replaced with a thiophene moiety. It is well known that bioisosteric relationship exists between benzene and thiophene ring where "CH=CH" is equivalent to 'S'. The 3rd chapter of thesis describes the synthesis of some hitherto unknown doubly condensed naphthoquinones: 9-methylnaphtho[1,2-*b*]furan[7,8-*b*]thiophene-4,5-dione (**9**), 9-methylnaphtho[2,1-*b*]furan[7,8-*b*]thiophene-4,5-dione (**16**), 9-methylnaphtho[1,2-*b*:7,8-*b*`]bisthiophene-4,5-dione (**23**) and 9-methylnaphtho[2,1-*b*:7,8-*b*`]bisthiophene-4,5-dione (**30**) in which ring A of phenanthro[4,3-*b*]furan-4,5-dione (the core nucleus of Isotanshinone-II) has been replaced with a 2-methylthiophene moiety whereas ring D has been modified with either a furan or a thiophene moiety (fig. 1). We believe that, the studies on the biophysical and biological properties of such doubly condensed

napthoquinones may contribute to significant information and may also throw some light on structure-activity relationship as well as mutagenic and antibacterial activities.

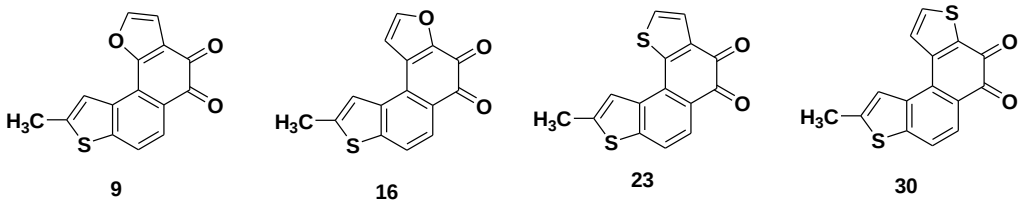
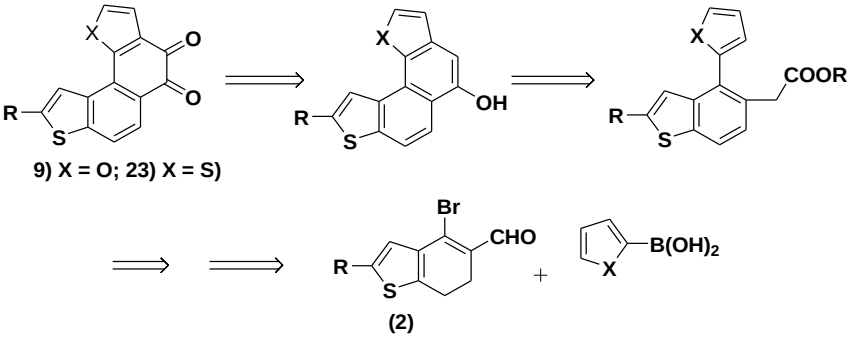


Figure 1: *bis*(heteroannulated)naphthoquinones 9, 16, 23 and 30

The furan analogue (**9**) may be considered as bioisoster of Isotanshinone-II nucleus. While the thiophene analogue (**23**) may be considered as bioister of thienophenanthraquinone. The other two compounds (**16** and **30**) are also the nuclear analogues of "U" shaped furophrenanthraquinone. The compounds have been synthesised with expectation to show potential antibacterial activity.

Plan of work

The retrosynthesis of doubly condensed naphthoquinones (**9** and **23**) has been outlined in scheme 1**.** The target molecules can be synthesised starting from 4-bromo-6,7-dihydro-2-methylbenzo[*b*]thiophene-5-carbaldehyde (**2**) **(**which may be obtained from 6,7-dihydro-2-methylbenzo[b]thiophen-4(5H)-one[7] *via* Vilsmeier-Haack reaction) and 2-furanboronic acid or 2-thiopheneboronic acid .



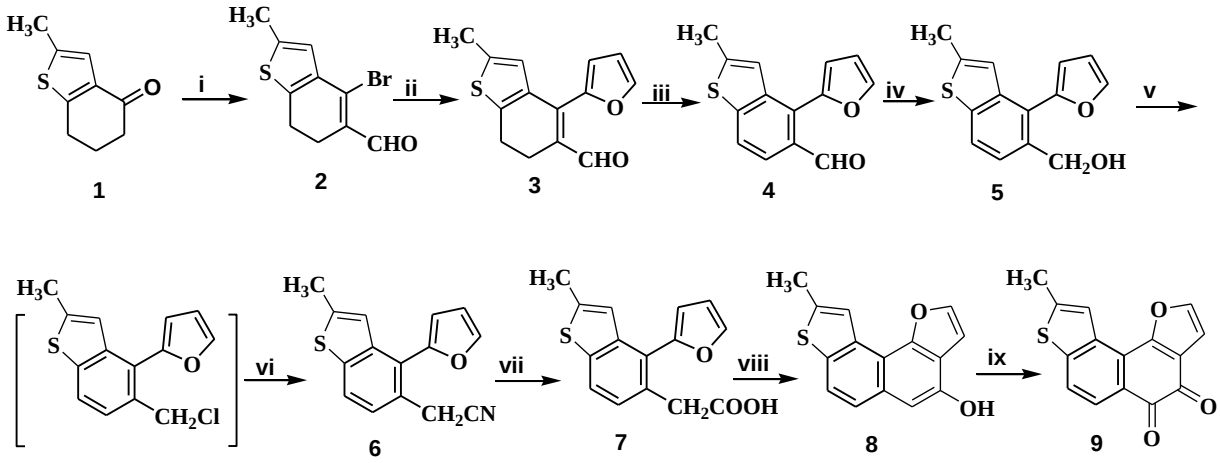
Scheme 1: Retrosynthesis of doubly condensed naphthoquinone derivatives 9 and 23

Present work: Results and discussions

The bromoaldehyde (**2**) was prepared in high yield, by reaction the ketone with PBr_3, DMF in $CHCl_3$. As usual Suzuki Reaction of compound **2** with 2-furanboronic acid furnished compound **3** in 63 % yield. Subsequent aromatisation, side chain homologation of CHO to

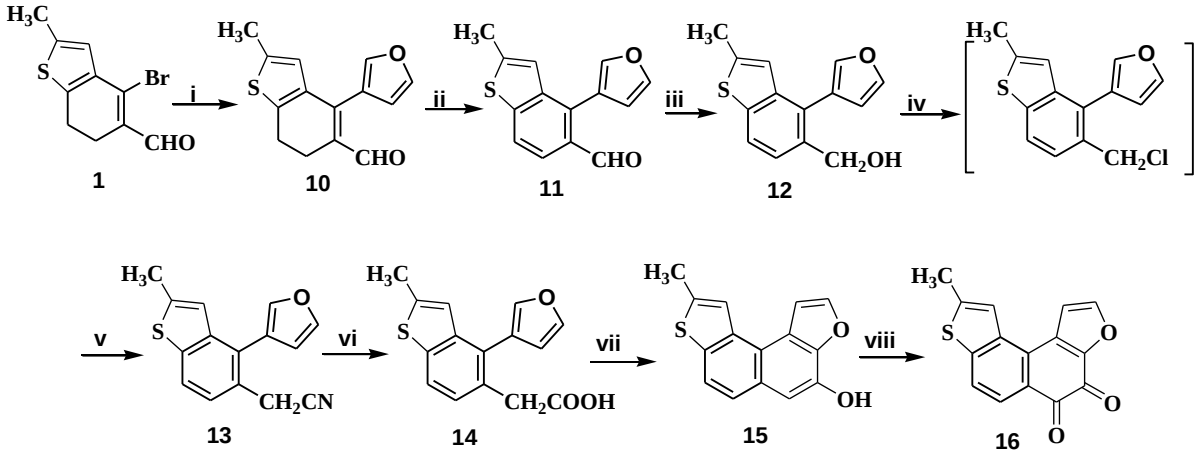
CH_2COOH produced carboxylic acid (**7**) in overall good yields. Cyclisation of the acid **7** furnished the phenolic intermediate **8**, oxidation (with Fremy's salt) of which resulted in formation of the target compound **9** to complete the synthesis (scheme 2). In a similar way starting from the bromoaldehyde (**2**) and 3-furanboronic acid synthesis of compound **16** was executed (scheme 3).

Synthesis of other *bis* thiophene condensed naphthoquinones (**23** and **30**) were achieved as per scheme 4 and scheme 5 using 2-thiopheneboronic acid and 3-thiopheneboronic acid respectively instead of 2/3-furanboronic acids.



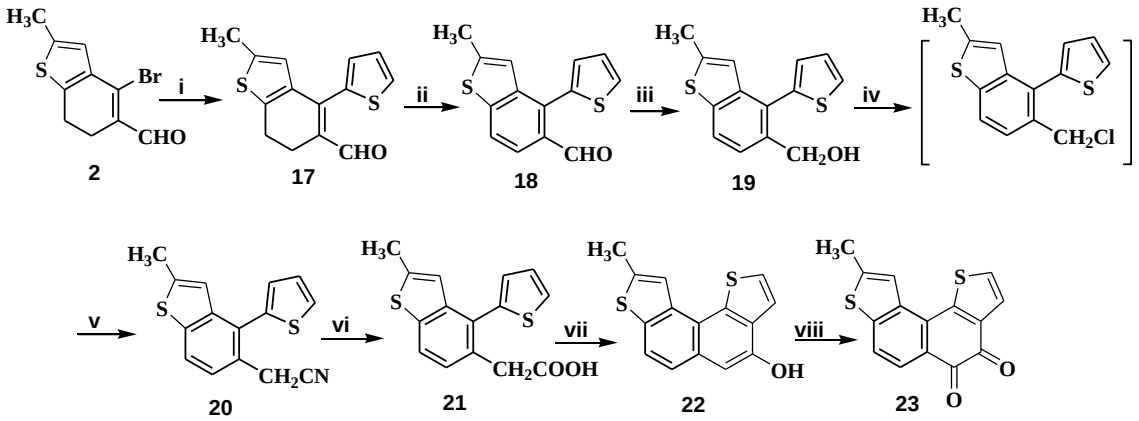
Reagents and Conditions: i) PBr_3, DMF, $CHCl_3$, 0 °C-r. t.,16 hrs, 73 %; ii) 2-furanboronic acid, $Pd(PPh_3)_4$, Et_3N, DMF, 110 ^oC, N_2 atm., 15 hrs, 63 %; iii) DDQ, benzene, reflux, 27 hrs, 87 5; iv) $NaBH_4$, EtOH, r.t., 2hrs, 92 %; v) MsCl, LiCl, *s*-Collidine, DMF, 0 °C, overnight; vi) KCN, DMF, 7 hrs, 68 %; vii) KOH, EtOH-H_2O, reflux, 21 hrs, 39 %; viii) TFAA-TFA, 0 °C, overnight, 84 %; ix) Fremy's salt, 1/6M Na_2HPO_4 buffer solution, MeOH, 0-5 °C, overnight, 79 %.

Scheme 2: Synthesis of 9-methylnaphtho[1,2-*b*]furan[7,8-*b*]thiophene-4,5-dione



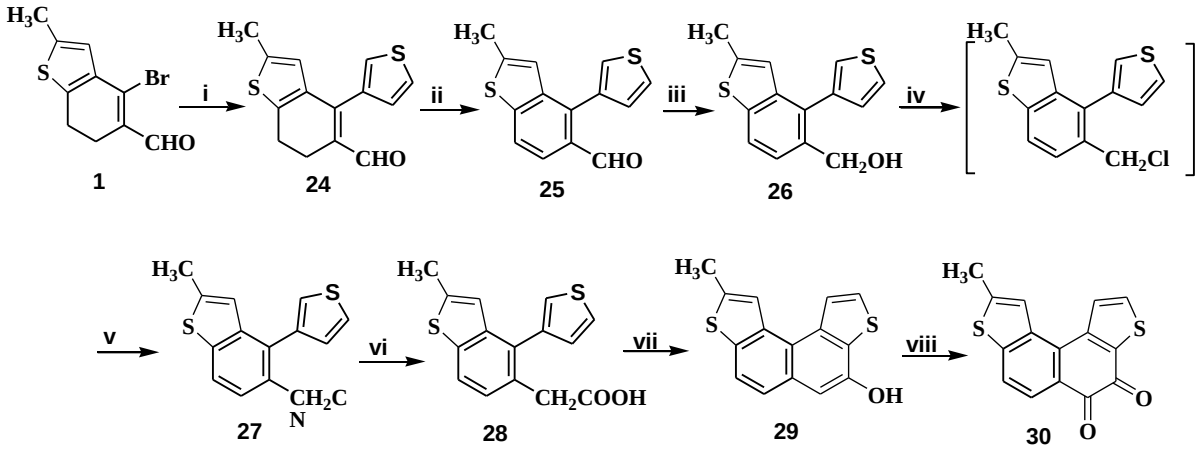
Reagents and Conditions: i) 3-furanboronic acid, $Pd(PPh_3)_4$, Et_3N, DMF, 110 ^oC, N_2 atm., 12 hrs, 67 %; ii) DDQ, benzene, reflux, 24 hrs, 89 %; iii) $NaBH_4$, EtOH, r.t., 2hrs, 92 %; iv) MsCl, LiCl, *s*-Collidine, DMF, 0 °C, overnight; v) KCN, DMF, 10 hrs, 76 %; vi) KOH, EtOH-H_2O, reflux, 23 hrs, 43 %; vii) TFAA-TFA, 0 °C, overnight, 85 %; viii) Fremy's salt, 1/6M Na_2HPO_4 buffer solution, MeOH, 0-5 °C, overnight, 86 %.

Scheme 3: Synthesis of 9-methylnaphtho[2,1-*b*]furan[7,8-*b*]thiophene-4,5-dione



Reagents and Conditions:i) 2-thiopheneboronic acid, $Pd(PPh_3)_4$, Et_3N, DMF, 110 ^oC, N_2 atm., 10 hrs, 61 %; ii) DDQ, benzene, reflux, 24 h, 86 %; iii) $NaBH_4$, EtOH, r.t., 2hrs, 91 %; iv) MsCl, LiCl, *s*-Collidine, DMF, 0 °C overnight; v) KCN, DMF, 11 hrs, 84 %; vi) KOH, EtOH-H_2O reflux, 20 hrs, 50 %; vii) TFAA-TFA, 0 °C overnight, 80 %; viii) Fremy's salt, 1/6M Na_2HPO_4 buffer solution, MeOH, 0-5 °C, overnight, 77 %.

Scheme 4: Synthesis of 9-methylnaphtho[1,2-*b*:7,8-*b*`]bisthiophene-4,5-dione



Reagents and Conditions: i) 3-thiopheneboronic acid, $Pd(PPh_3)_4$, Et_3N, DMF, 110 ^oC, N_2 atm., 10 hrs, 67 %; ii) DDQ, benzene, reflux, 24 h, 89 %; iii) $NaBH_4$, EtOH, r.t., 2hrs, 96 %; iv) MsCl, LiCl, *s*-Collidine, DMF, 0 °C overnight; v) KCN, DMF, 11 hrs, 89 %; vi) KOH, EtOH-H_2O reflux, 20 hrs, 58 %; vii) TFAA-TFA, 0 °C overnight, 93 %; viii) Fremy's salt, 1/6M Na_2HPO_4 buffer solution, MeOH, 0-5 °C, overnight, 83 %.

Scheme 5: Synthesis of 9-methylnaphtho[2,1-*b*:7,8-*b*`]bisthiophene-4,5-dione

All the novel compounds have been characterised by ^1H NMR, ^{13}C NMR, IR, HRMS etc. Tentative analysis of ^1H NMR spectral data of *o*-quinonoes **9, 16, 23** and **30** are depicted in fig. 2.

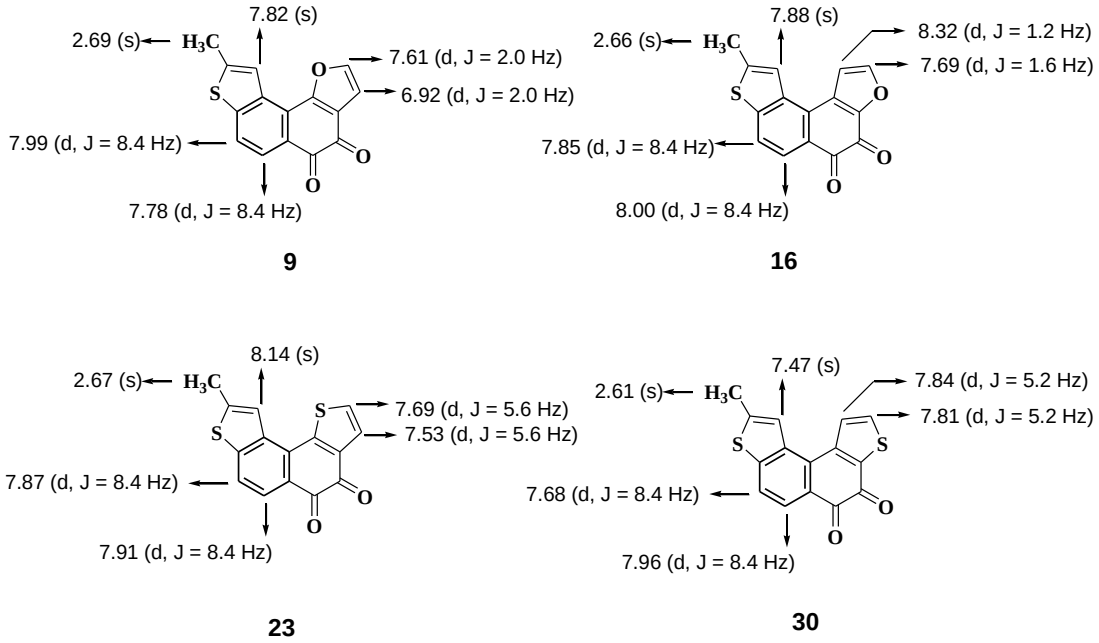


Figure 2: Tentative assignments of ^1H NMR spectral data of the *o*-quinones 9, 16, 23 and 30

Conclusion

Thus, we have synthesised a total of four novel "U" shaped doubly condensed (with thiophene and furan moieties) naphthoquione derivatives. Modifications have been made in the ring A or ring A and D both of the core nucleus present in natural occurring furophenanthraquinone: Isotanshinone-II. The process involved a diversity oriented synthesis. In future, the boronic acid components can be replaced with substituted 2/3-thiopheneboronic acid derivatives as well as substituted 2/3-furanboronic acid derivatives to prepare a compound library of several doubly condensed naphthoquinones. Ring A may also be substituted with other heterocyclic rings to obtain more novel *bis* annulated napthoquinones as an application of this methodology. Biological evaluations of the synthesised compounds are under progress as collaborative work with other research group.

References

1. J. Acuna, J. Piermattey, D. Caro, S. Bannwitz, L. Barrios, J. Lopez, Y. Ocampo, R. V. Reyes, F. Aristizabal, R. Gaitan, K. Muller, L. Franco, *Molecules* **2018**, *23*, 186 (1-21).
2. J. H. Gao, R. J. Li, L. Q. Li, Q. Ming, H. Jiang, H. X. Li, W. P. Hu, *Adv. Mater.* **2007**, *19*, 3008.
3. V. A. Bren, A. D. Dubonosov, V. I. Minkin, A. V. Tsukanov, T. N. Gribanova, E. N. Shepelenko, Y. V. Revinsky, V. P. Rybalkin, *J. Phys. Org. Chem.* **2001**, *20*, 917.
4. G. Ferrara, T. Jin, M. Akhtaruzzaman, A. Islam, L. Han, H. Jiang, Y. Yamamoto, *Tetrahedron Lett.* **2012**, *53*, 1946.
5. N. Yanai, T. Mori, S. Shinamura, I. Osaka, K. Takimiya, *Org. Lett.* **2014**, *16*, 240.
6. G. Shukla, A. Srivastava, D. Yadav, M. S. Singh, *J. Org. Chem.* **2018,** *83,* 2173.
7. N. P.Buu-Hoi, N. Hoan, N. H. Khoi, *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1053.

Poster presentations:

1. "***Search for novel antibacterial: Synthesis of doubly condensed naphthoquinone derivatives as "AD"-ring modified Isotanshinone-II analogue***" Aparna Sarkar, Ankita

Dey, Gandhi K. Kar; *International Conference on Advancement in Science and Technology (ICAST-2018)*, **2018**; Visva-Bharati University, Santiniketan, W.B, India .

2. "***Nuclear modification of "A-ring" of the core nucleus of Isotanshinone-II in search for novel antibacterials: Synthesis of doubly condensed naphthoquinone derivative 9-methylnaphtho[1,2-b]thieno[7,8-]furan 4,5-dione & it's analog as bioisoster***" Aparna Sarkar, Debjani Maiti, Gandhi K. Kar; *Proceedings of the International Conference on Chemistry for Human Development (ICCHD 2018),* **2018**, Calcutta University and Heritage Institute of Technology, Kolkata, W. B. India.

List of publication in peer reviewed international Journals:

1. *"Thiophene Analogue of Isotanshinone-II Nucleus: A Novel Approach towards the Synthesis of Phenanthro[4,3-b]thiophene-4,5-dione and Phenanthro[3,4-b]thiophene-4,5-dione Derivatives"* Aparna Sarkar, Rumpa Das, and Gandhi K. Kar; **ChemistrySelect 2018**, 3, 11422– 11426.

2. *"A Suzuki-Coupling-Based Generalized Route for the Synthesis of 2-(2/3-thienyl)-cycloalk-1-ene-1-carbaldehydes as Precursors for Condensed Thienophenanthraquinones"* Aparna Sarkar, Rumpa Das, Gandhi K. Kar; **Synlett. 2018,** *29*, 344-348.

Paper presented in National / International Symposium / Conferences:

1. *"Search for novel antibacterial: Synthesis of doubly condensed naphthoquinone derivatives as "AD"-ring modified Isotanshinone-II analogue"* Aparna Sarkar, Ankita Dey, Gandhi K. Kar. poster presentation in *International Conference on Advancement in Science and Technology (ICAST-2018)*, 3-4th September, **2018** at Visva-Bharati University, Santiniketan,West Bengal, India organized by the Indian JSPS Alumni Association in association with the Department of Physics, Visva-Bharati.

2. *"An approach towards the synthesis of phenanthro[4,3-b]thiophen-4,5-dione derivatives as thiophen analogue of core nucleus of Isotanshinone-II isolated from Salvia species"* Aparna Sarkar, Gandhi K. Kar; oral presentation in *"National Symposium on contribution of Women in Science in India (NSCWSI 2018)"*, organized by Indian Science News Association (ISNA) at Calcutta University, Feb. 15-16, **2018**.

3. *"Nuclear modification of "A-ring" of the core nucleus of Isotanshinone-II in search for novel antibacterials: Synthesis of doubly condensed naphthoquinone derivative 9-methylnaphtho[1,2-b]thieno[7,8-]furan 4,5-dione & it's analog as bioisoster"* Aparna Sarkar, Debjani Maiti, Gandhi K. Kar; poster presentation in *Proceedings of the International Conference on Chemistry for Human Development (ICCHD 2018)*, 2018 (Jan. 8-10, **2018**), Organized by Calcutta University and Heritage Institute of Technology, Kolkata,W. B. India.

4. *"Model studies towards the synthesis of Isotanshinone-II: General method for synthesis of some angularly fused novel "U" Shaped furoquinones simulating ABCD rings of Isotanshinone-II"* Aparna Sarkar, Rumpa Das, Khokan Samanta, Gandhi K. Kar; oral presentation in *Proceedings of the National Symposium on Recent Advances in Chemistry and Industry* (**2015**); Indian Chemical Society, Calcutta University, Kolkata.

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